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Review

Beyond MADIT

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ABSTRACT

Sudden cardiac death remains the global burden. The most common associated arrhythmia is ventricular fibrillation. From current guidelines, defibrillation is the most critical step to rescue the cardiac arrest victims. Internal defibrillators were invented for prompt treating the ventricular arrhythmia. The MADIT trial the benchmark randomized controlled trial that demonstrated the efficacy of defibrillators for sudden death protection and not only that MADIT-RIT which addresses the issue of inappropriate therapy with ICD and MADIT-CRT which highlights the importance of biventricular pacing in patients with cardiomyopathy with mild heart failure symptoms. Hereby, we review the articles the MADIT trials.

Contents

1. Introduction

Sudden cardiac death (SCD) has remained unsolved global problem. The actual rate of sudden death is still incompletely defined, and varies among the studies; however, the most widely cited estimation is in the range of 300,000–350,000 cases annually [1].

In recent prospective studies using multiple sources in the United States, Netherlands, Ireland, and China [2–4], SCD rates range from 50 to 100 per 100,000 in the general population [3]. Regional incidence of SCD has periodically been reported. The incidence of SCD in Europe is around one per 1000 population per year [2], similar to those in US. In Asia, data from Japan showed a similar incidence to that seen in the US and Europe, with the annual rate estimated to be 1–2 per 1000 population per year [5]. In China, from a project involving four major cities the annual incidence of SCD was estimated to be 0.42 per 1000 population [4]. In Hong Kong, the SCD incidence rate was found to be only 0.018 per 1000 population [3].

Malignant ventricular arrhythmia is the most commonly rhythm abnormality (80%) in patients with cardiac arrest [6,7]. Other bradyarrhythmias were also found associated with sudden death [6–10]. Prompt recognition and cardiopulmonary resuscitation save life in cardiac arrest patients, and external defibrillation is the most critical step to treat ventricular arrhythmia. This scheme has been adopted to the national guideline for patients who suffer from cardiac arrest. Due to success in treating ventricular arrhythmia, the implantable automatic defibrillators (ICD) were introduced for treating ventricular arrhythmia by Mirowki et al. [11]. Winkle et al. and Fogoros et al. have first shown the efficacy of ICDs in treating ventricular arrhythmia

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[12,13]. However, both studies were not randomized or controlled. Apart from SCD protection, there have been subsequent studies regarding the utilities of ICDs. In this review, we discuss the prototype randomized controlled trials (MADIT trials) that studied the efficacy of ICDs and its applications.

2. MADIT trial

In early 1980, the Multicenter Post-infarction Research Group reported the declination of left ventricular function associated with the increase in the one-year cardiac mortality, with exponential relationship when ejection fraction less than 0.35 [14]. Non-sustained ventricular tachycardia, ventricular dysfunction and coronary artery disease were found to increased risk of sudden death. Buxton et al. have shown left ventricular ejection fraction is the strongest predictor for sudden cardiac death [15]. They have also shown that inducible VT significantly predicts the risk of death in patients with coronary artery disease [15]. Bigger et al. confirmed that unsustained ventricular tachycardia was associated with 30% two-year mortality rate in patient with coronary artery disease [16]. Antiarrhythmic drugs have been widely used to treat for non-sustained ventricular tachycardia; however, the survival benefit from antiarrhythmic therapy has not been proven [17]. Previous findings from major trial suggested that antiarrhythmic drugs class IC increased cardiac mortality in patients with coronary artery disease [18]. From these outcomes, the need for ICD trials was heightened to address the efficacy of sudden death prevention in these high-risk patients. The Multicenter Automatic Defibrillator Implantation Trial (MADIT or MADIT-I trial) was initiated in 1991 [19,20]. This was the first trial that demonstrated the role of ICD for primary prevention of SCD in asymptomatic patients with ischemic cardiomyopathy.

MADIT trial enrolled 196 adult patients with prior myocardial infarction more than 3 weeks (Q wave or elevated cardiac enzyme), with non-sustained ventricular tachycardia (a run of 3–30 of ventricular ectopic beats with a rate more than 120 beats per minute), with left ventricular ejection fraction less than or equal to 0.35, and NYHA class I–III. The trial excluded patients with coronary artery bypass grafting within 2 months or coronary angioplasty within 3 months prior to the study. Wilber et al. had found patients with coronary artery disease with abnormal ventricular function had 50% incidence of sudden death in 2 years if ventricular arrhythmia were inducible, and the inducibility of ventricular arrhythmia was a significant independent predictor for sudden death [21]. From this study, the inducibility of ventricular arrhythmia was included in eligibility criteria. The primary end-point was the all-cause mortality. The study compared the primary outcomes in patients with ICD versus conventional therapy. Termination of trial was initiated when 51 deaths were reported, and the efficacy boundary of sequential design was crossed.

Major outcomes from MADIT trial suggested that the risk of death in defibrillator group was significantly less than conventional-therapy group with hazard ratio of 0.46. This over-all mortality reduction was contributed from reduction in cardiac death. However, there was no explanation why more patients with a defibrillator in the study died from non-arrhythmia causes than patients without a defibrillator. This was postulated from investigators that it might because of misclassification of the cause of death [20]. From this trial, ICD was approved for indication for primary prevention in high-risk patients.

This trial had been criticized in several aspects, since it was published in 1996. Moreover, another similar cohort, The Multicenter Unsustained Tachycardia Trial (MUSTT), was often compared to MADIT [22]. One of the important differences was that beta-blockers were used in 16% in patients in MADIT trial, as compared to 40% in MUSTT trial. The imbalance of beta-blocker use favored ICD-treated patients in MADIT trial (15% control group, 26% ICD group), as compared with MUSTT, which favored the control group (51% control group, 34% ICD group). However, both trials showed the similarity of the outcomes in that the mortality reduction was observed particularly in ICD-treated patients. The absence of untreated group in MADIT trial was also discussed that this could be attributed to harm caused by antiarrhythmic drug in conventional group [23]. The “conventional group” was also questioned. This group was suggested to confine with non-antiarrhythmic therapy, and in fact, there was marked variability in management in this group—the choice of treatment was on physician's decision. The other important limitation is the reproducibility of ventricular arrhythmia. Senges et al. found that non-sustained ventricular tachycardia on Holter monitor in patients fulfilling MADIT criteria had limited clinical value in patient selection for programmed ventricular stimulation [24].

3. MADIT-II

Electrophysiological testing has been used to identify who is at risk of sudden cardiac arrest, but its utility in patients with coronary artery disease and left ventricular dysfunction remains uncertain. In addition, electrophysiological testing in MADIT trial could possibly select the high-risk patients who less likely to be respond to antiarrhythmic drug therapy [25]. In addition, two-year mortality rate is in the range of 20% in patients with coronary artery disease with ejection fraction less than or equal to 0.30, with the optimal therapies [26]. From above reasons, MADIT-II did not include electrophysiologic testing for selection criteria. Moss et al. initiated MADIT-II in 1999 [27]. This trial enrolled 1232 patients with prior myocardial infarction more than 4 weeks (Q wave or elevated cardiac enzyme), with left ventricular ejection fraction less than or equal to 0.30, and NYHA class I–III. The trial excluded patients with coronary artery bypass grafting or coronary angioplasty within 3 months prior to the study. Repetitive ventricular ectopy was eliminated from inclusion criteria after the study began because almost all eligible patients had such arrhythmia. Primary outcome was death from any causes.

Major outcomes from MADIT-II trial suggested that, once again, the risk of death in defibrillator group was significantly less than conventional-therapy group with hazard ratio of 0.69. In this trial, the major drawback was corrected. The medication use remained balanced between ICD patients, and conventional therapy patients. The size of study population was greater in the latter study. However, hazard ratio of rate of death in the latter trial was higher than the former one. This was mentioned to be due to the lower cutoff of ejection fraction, more vigorous medication [28]. Interestingly, the rate of heart failure hospitalization was unexpectedly high in ICD patients (20% versus 15%). The explanation was uncertain, but was thought to be due to (1) multiple shocks leading to myocardial injury; (2) higher incidence of heart failure progression in ICD patients with longer life span; (3) right ventricular pacing adversely impacting ventricular synchrony.

MADIT-II trial was designed without risk stratification, targeting broad range of population. Several subgroup analyses from MADIT-II have been published after the main trial. The advantage of ICD in lowering mortality risk depends on time since the most recent myocardial infarction [29]. The longer after myocardial infarction is associated with the greater mortality reduction. ICD was equally beneficial in diabetic and non-diabetic patients [30]. In addition, age seems not to impact on the mortality benefit from ICD, even though elderly patients, older than 75 years old, were marginally benefitted from ICD [31]. Dhar et al. also showed the QRS duration associated with SCD in non-ICD patients; however, it

was not related with SCD and ventricular tachyarrhythmia in ICD patients [32]. However, patients with advanced renal dysfunction do not received the protective effect from ICD [33].

4. MADIT-CRT

The heart failure event in the MADIT-II trial led to the MADIT-CRT. The similar outcomes were found in SCD-HeFT and DEFINITE trials [34]. From prior study, Bristow et al. demonstrated the mortality reduction from CRT-D and CRT-P as compared to medical therapy alone. However the patients included in this trial were in NYHA class III and IV [35]. This trial was designed in 2005 aiming at patients with NYHA class I and II for preventive purposes [36].

One thousand eight hundred patients were included (consisting of ischemic or non-ischemic cardiomyopathy, a QRS duration more than or equal to 130 ms, NYHA class I, II, ejection fraction less than or equal to 30%). These patients were randomized to ICD plus CRT, or ICD alone. Due to the adverse effect of right ventricular pacing, a lower rate limit was set at 40 beats per minute both groups. Primary outcome was assessed for composite of death or non-fatal heart failure.

The primary outcome occurred 17.2% in ICD plus CRT patients as compared to 25.3% in ICD only patients, with hazard ratio of 0.66. This risk reduction was attributed by 41% reduction in the risk of heart failure. The hazard ratios for primary end points in ischemic and non-ischemic cardiomyopathy patients were similar. In subgroup analyses, it suggested that CRT-D had equal mortality benefit in each subgroup (regardless of ejection fraction, age, LVESV, LVEDV, NYHA class). Nevertheless, women had greater mortality reduction than men, and this CRT-D will reduce mortality only in patients with QRS width more than or equal to 150 ms. This major outcome seemed to be confirmed with REVERSE trial [37].

5. MADIT-RIT

Growing number of ICD trials lead to the popularity of ICD implantation. Inappropriate therapy from ICD has become a problem in clinical practice. Supraventricular tachyarrhythmia remained the most common rhythm causing inappropriate therapy despite the proper ICD programming. Major adverse consequences' following inappropriate therapy includes pain, anxiety, a poor quality of life, proarrhythmia [38,39]. In addition, this could trigger fatal arrhythmia. Even though, dual-chamber ICD's are implanted twice as frequently as single chamber ICD's due to proper rhythm detection and differentiation, no randomized controlled trial has shown that proper ICD programming for reducing inappropriate therapy would affect the clinical outcomes. This trial was initiated in 2012 to determine appropriate ICD programing [40].

This trial included 1500 patients, who met the ICD criteria for primary prevention (non-ischemic, ischemic, dual chamber ICD or CRT-D). The patients were randomized to 3 arms: (1) conventional therapy: Zone 1(VT) 170 bpm, 2.5 s delay, Zone 2 (VF) 200 bpm, 1 s delay; (2) high rate therapy: Zone 1(VT) 170 bpm, monitor only, Zone 2 (VF) 200 bpm, 2.5 s delay; (3) long delay therapy: Zone 1 (VT) 170 bpm, 60 s delay, Zone 2 (VT) 200 bpm, 12 s delay, Zone 3 250 bpm, 2.5 s delay. Primary outcomes were assessed as the first occurrence of inappropriate therapy (ATPs or shocks), The secondary end points were assessed as death from any cause and the first episode of syncope.

Primary outcomes were found as high-rate group and long-delay group had significantly greater risk for device therapy than conventional therapy with 79% and 76% risk reduction respectively. Mortality reduction also was shown in high-rate group and long-delay group with 55% and 44% risk reduction. With previous concern of syncope with delay treatment, the similar rate of syncope episodes was demonstrated in each patient group. With lower rate of inappropriate therapy, it was suggested that ventricular tachyarrhythmia detected by ICD could possibly terminated spontaneously without unnecessary treatment. However, the reason for reducing mortality in the trial remains unclear.

The MADIT-RIT study enrolled only primary-prevention patients. An earlier study, PainFREE Rx II, explored the over-all rates of inappropriate therapy in both primary and secondary prevention patients [41]. Both groups had a 15% rate of inappropriate therapy, but these were slightly more common in primary-prevention patients. Of all the arrhythmic events detected and treated by the ICD, 46% led to inappropriate therapy in primary-prevention patients compared to 34% in secondary-prevention patients. With secondary-prevention patients, clinicians have arrhythmic history to help guide programming decisions.

The MADIT-RIT study found that high-rate and delayed-therapy were both effective in reducing inappropriate shock and mortality compared to conventional therapy. Since they are both effective, the simpler one should take precedence. Programming a cutoff rate of 200 bpm is very straightforward (and much easier to program than delayed therapy) and MADIT-RIT found it reduced both inappropriate therapy and mortality rates. Program a high VF cutoff (for example, 200 bpm) and delay the onset of the therapy — MADIT-RIT shows that this saves lives.

6. Future direction

Although “MADIT” studies have proven benefits from ICDs, no randomized controlled have been created for the certain patient subgroups. It remains unclear whether all patients with similar profiles (to inclusion criteria) in cohorts would gain similar benefit from ICDs. In addition, results from previous studies for risk stratification have not been consistent, and could not be applicable reliably to general population or to ICD candidates. Some questions, which remain unanswered with “MADIT” studies, were whether the patients with advanced heart failure and narrow QRS complex, do they benefit from biventricular pacing? Two prospectively designed, yet moderately large, studies in patients with advanced HF and normal QRS complex have been completed, the ReThinQ [42] and ESTEEM-CRT [43] trials; both studies missed the primary end-point and turned out to be negative. What about patients with moderate LV dysfunction and need for RV pacing? HOBIPACE [44] and PAVE [45] studies show that patients with preexisting mild to moderate left ventricular dysfunction and an indication for standard pacing have improved left ventricular systolic function, exercise capacity, and quality of life after biventricular pacing compared with right ventricular apical pacing. These results suggest that biventricular pacing may be a feasible option for permanent pacing in the majority of patients who have normal left ventricular systolic function and that it may attenuate the adverse effects of conventional right ventricular apical pacing on left ventricular systolic function. This hypothesis has been recently tested in the PACE trial [46]. The study was a double-blinded, multicenter study, in which 177 patients were assigned to either biventricular pacing (89 patients) or right ventricular apical pacing (88 patients). The PACE study showed that mean LVEF declined by almost 7 percentage points (from 61.5 ± 6.6 to 54.8 ± 9.1) in the first year of right ventricular apical pacing in patients with a normal ejection fraction. There are several limitations of this study: the sample was small, and the study was not powered to detect significant differences in clinical events.

The increased cost and complications associated with biventricular pacemakers are potential concerns. Randomized trials with longer follow-up periods, larger samples, and sufficient power to evaluate clinical outcomes between these two pacing strategies are warranted. Even though, the cost of ICDs has come down, financial restrain has not yet been resolved in the new healthcare reform. These questions would be important challenges and would probably be answered in the future trial with the least cost and the most survival implication in the clinical practice.

Conflict of interest

None.

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